



**University of
Zurich**^{UZH}

**Zurich Open Repository and
Archive**

University of Zurich
University Library
Strickhofstrasse 39
CH-8057 Zurich
www.zora.uzh.ch

Year: 2014

Risks and benefits of cardiac imaging: an analysis of risks related to imaging for coronary artery disease

Knuuti, Juhani ; Bengel, Frank ; Bax, Jeroen J ; Kaufmann, Philipp A ; Le Guludec, Dominique ;
Perrone Filardi, Pasquale ; Marcassa, Claudio ; Ajmone Marsan, Nina ; Achenbach, Stephan ; Kitsiou,
Anastasia ; Flotats, Albert ; Eeckhout, Eric ; Minn, Heikki ; Hesse, Birger

DOI: <https://doi.org/10.1093/eurheartj/eh512>

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-92274>

Journal Article

Published Version

Originally published at:

Knuuti, Juhani; Bengel, Frank; Bax, Jeroen J; Kaufmann, Philipp A; Le Guludec, Dominique; Perrone Filardi, Pasquale; Marcassa, Claudio; Ajmone Marsan, Nina; Achenbach, Stephan; Kitsiou, Anastasia; Flotats, Albert; Eeckhout, Eric; Minn, Heikki; Hesse, Birger (2014). Risks and benefits of cardiac imaging: an analysis of risks related to imaging for coronary artery disease. *European Heart Journal*, 35(10):633-638.

DOI: <https://doi.org/10.1093/eurheartj/eh512>

Risks and benefits of cardiac imaging: an analysis of risks related to imaging for coronary artery disease

Juhani Knuuti^{1*}, Frank Bengel², Jeroen J. Bax³, Philipp A. Kaufmann⁴, Dominique Le Guludec⁵, Pasquale Perrone Filardi⁶, Claudio Marcassa⁷, Nina Ajmone Marsan³, Stephan Achenbach⁸, Anastasia Kitsiou⁹, Albert Flotats¹⁰, Eric Eeckhout¹¹, Heikki Minn¹², and Birger Hesse¹³

¹Turku PET Centre, University of Turku and Turku University Hospital, Turku, Finland; ²Klinik für Nuklearmedizin, Medizinische Hochschule, Hannover, Germany; ³Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands; ⁴Cardiac Imaging, University Hospital Zurich, Zurich, Switzerland; ⁵Department of Nuclear Medicine, Bichat-Claude Bernard Hospital, AP-HP, Inserm U698; and Paris Diderot University, Paris, France; ⁶Department of Advanced Biomedical Sciences Cardiology Section, Federico II University of Naples, Naples, Italy; ⁷Department of Cardiology, S. Maugeri Foundation, IRCCS, Scientific Institute of Veruno, Veruno, Italy; ⁸Department of Cardiology, University of Erlangen, Erlangen, Germany; ⁹Cardiology Department, Sismanoglio Hospital, Athens, Greece; ¹⁰Nuclear Medicine Department, Universitat Autònoma de Barcelona, Hospital de la Santa Creu, Sant Pau, Spain; ¹¹Service of Cardiology, CHU Vaudois, University of Lausanne, Lausanne, Switzerland; ¹²Department of Oncology and Radiotherapy, University of Turku, Turku, Finland; and ¹³Clinic of Clinical Physiology, Nuclear Medicine and PET, Rigshospitalet, Copenhagen, Denmark

Received 31 May 2013; revised 18 October 2013; accepted 21 November 2013; online publish-ahead-of-print 29 December 2013

Introduction

The potential risks associated with cardiovascular imaging (CVI) have recently been debated, partly triggered by the rapid increase in the use of imaging procedures and new imaging modalities such as cardiac computed tomography (CT).^{1,2} The discussion has mainly focused only on a single-risk aspect such as radiation.³ However, the various procedures have several risks: stressors, contrast agents, invasiveness, radiation, etc. Even more important, the test must be related to the benefit of performing or not performing the test with the risk and drawbacks associated with the disease remaining undetected.

We aimed to create a balanced analysis of immediate, short- and long-term risks associated with CVI in relation to the natural course of coronary artery disease (CAD) and to therapeutic interventions. The imaging tests for CAD were selected, since many CVI tests are commonly used. We analysed: (i) the risk of major cardiac events (MCEs) for each component of imaging test; (ii) the upper limit for each risk, in order to avoid underestimation of a risk; (iii) composite risks calculated for selected common diagnostic tests for CAD; (iv) the risks compared with the risk of the disease itself, to assess the potential benefits of tests; and (v) comparison with risks in regular life activities and that associated with trivial long-term prophylactic interventions such as aspirin use.

This analysis is based on the data available from the literature. Data for risks related to some of the procedures are quite limited, for some variable, and for some of limited quality. Still we sought to present risk estimations from all the procedures using reliable studies and databases available from an extensive search of the literature. The

detailed information about risk assessments is shown in Supplementary material.

Analysis of risks

Definitions

In the literature, risks are described in many different ways, e.g. 'fatal, major, serious, less severe, and milder'. In the present analysis, we use 'fatal', when presented as such in the literature. 'MCEs', often used in the investigations, are presented quoting the descriptions of the citations. The degree of seriousness for 'less serious or minor adverse or side effects' vary significantly in the citations referred. In this analysis, they are defined as complications or side effects that are not life threatening. 'Adverse events (AEs) (serious and less serious) and adverse drug reactions' in relation to drug administration are described according to the WHO definitions.⁴

Stress tests

Dynamic exercise and different pharmacological stress agents including vasodilators (adenosine, dipyridamole, selective A2A receptors agonists) and inotropic-chronotropic agents (dobutamine) are employed. The overall hard events rate of dynamic exercise has been reported to be in the range of 1.2–8.6/10 000 tests, depending on the referring population.^{5,6} The overall hard event rate of pharmacological stress with dipyridamole or adenosine is comparable with that of exercise,^{7,8} but minor side effects are more common. Recently, A2A selective agonists have been approved as stressors. The incidence of serious AEs and side effects appears significantly lower than with

The opinions expressed in this article are not necessarily those of the Editors of the *European Heart Journal* or of the European Society of Cardiology.

* Corresponding author. Tel: +358 500 592 998, fax: +358 2231 8191, Email: juhani.knuuti@utu.fi

Published on behalf of the European Society of Cardiology. All rights reserved. © The Author 2013. For permissions please email: journals.permissions@oup.com

adenosine.⁹ The complication rate with dobutamine, which is used commonly with stress echocardiography is higher than that reported for other stressors: One severe AE in 335 tests has been reported in a recent meta-analysis.^{10,11} For the purpose of this study, we used a fatal event rate of 1/20 000 for exercise and 1/10 000 for pharmacological stressors.

Imaging procedures

Cardiac magnetic resonance imaging

Strong static magnetic field as such is unlikely to cause significant adverse biological effects. RF energy applied to the body may be responsible for tissue heating.¹² Some metallic devices, e.g. pacemaker leads, may potentially induce excessive local heating as well as arrhythmias.¹³ Gradient magnetic fields could stimulate nerves and muscles, occasionally causing discomfort¹⁴ but current cardiac magnetic resonance imaging (CMRI) systems typically operate below nerve stimulation levels. Quickly changing magnetic fields may generate electrical currents in electrically conductive devices with potential risk of arrhythmia induction in patients with pacemaker leads.¹³ Ferromagnetic objects, including cerebral aneurysm clips, drug infusion pumps, cardiac pacemakers/defibrillators, accidentally introduced into a CMRI suite are quickly attracted towards the magnet and has been cause of significant injuries and even death of patients and CMRI operators. Significant increase of DNA double-strand breaks have been detected after routine 1.5 T cardiac MR examination^{15,16} but obviously more information about this phenomenon is needed to make any numerical estimation about this risk.

In this paper, we estimated accidents in 0.07/10 000 examinations and 0.2/10 000 other serious AEs, including burns, arrhythmias in CMRI studies. Since no data are currently available about the clinical events caused by MR-induced DNA damage, this risk was not included.

Echocardiography

Biological effects of diagnostic ultrasound have been documented in experimental studies conducted on molecular, cellular and animal level.¹⁷ The effects depend on the characteristics of the sound wave, sensitivity of exposed tissue, and time duration of exposure. The effects may broadly be classified into thermal and mechanical effects. With current diagnostic ultrasound technology, biological effects are unlikely to be caused directly by tissue heating.¹⁸

Among possible mechanical effects of ultrasound, a potential risk is cavitation: formation and rhythmic oscillation of microbubbles produced from gasses dissolved in living tissue. The mechanical index has been developed as predictor of acoustic cavitation and is displayed as a safety parameter on modern ultrasound scanners. Capillary rupture can be demonstrated when tissues containing gas-filled contrast agents are exposed to ultrasound,¹⁹ but so far there is no evidence of significant health risk from exposure to medical ultrasound for patients or clinical staff members.

Coronary angiography

Diagnostic invasive coronary angiography (CAG), like most invasive procedures, may cause serious complications.^{20,21} Major complications of 1–2% are reported (Table 1), the likelihood of major

complications increasing significantly with the severity of the underlying disease. Important predictors of major complications include shock, acute myocardial infarction of <24 h, unstable angina, cardiomyopathy, renal insufficiency, heart failure, and high age. Patients undergoing CAG in an emergency setting are at greatest risk for complications. The skill and experience of the operator and the catheterization laboratory staff, as well as the peri-procedural management and low-profile catheters are also important factors. Currently, the transradial approach decreases entry site complications as compared with the femoral approach.

In the current analysis, the acute risk of death by CAG was estimated to be 8/10 000 studies and the rate of serious AEs 177/10 000.^{20,21}

Contrast agents and tracers

Contrast agents for cardiac computed tomography and invasive coronary angiography (iodinated)

Computed tomography and invasive CAG requires injection of an iodinated contrast agent. Adverse events after use of contrast media include local effects (extravasation), acute or delayed reactions and contrast-induced nephropathy. Extravasation occurs in ~0.2% of procedures when a power injector is used²² and may lead to severe damage, including compartment syndrome. Mild general reactions occur in 0.4% of patients and serious reactions, including pulmonary oedema, severe hypotension, and loss of consciousness occur in 0.04%²³ with non-ionic contrast agents.

The most prominent risk of iodinated contrast agents is nephrotoxicity, rare in patients without a history or symptoms of renal disease. The incidence of kidney injury was 1.3% after percutaneous coronary intervention.²⁴ Nephropathy rates were substantially lower for intravenous compared with intra-arterial injections (1.1 and 1.8%, respectively).^{24–26} The additional mortality of patients with clinically significant kidney failure was reported as high as 14–15.8%.^{24–27}

For the purpose of this study, we estimated the rate of death due to acute general reactions for contrast agents as 0.059/10 000 and long-term risk due to nephropathy to be 6.6/10 000 for intravenous and 7.6/10 000 for intra-arterial administration. The rate of serious acute AEs was estimated to be 4.06 and long-term events 79.0 per 10 000 studies.

Contrast agents for echocardiography

Contrast agents in echocardiography are used for cardiac chamber opacification, in particular to improve the endocardial border of the left ventricle,²⁸ and evaluation of myocardial perfusion. The use of contrast agents improves diagnostic accuracy and reproducibility of both rest and stress echocardiography, including left ventricular volumes, ejection fraction, and wall motion assessment.^{28,29}

In the present analysis, we used a risk of serious AEs as 3/10 000 and the risk of death 0.1/10 000 after echo-contrast administration as suggested by the overall post-marketing experience with a perflutren lipid microsphere (Definity).³⁰ In our estimations, we assumed that contrast agents have been used in stress echo examinations.

Table 1 Complication rates/10 000 examinations during diagnostic cardiac catheterization

Death	MI	Stroke	Ventricular arrhythmia	Vascular	Contrast reaction	Total
8	5	7	10	20	70	177

MI, myocardial infarction.

Contrast agents for cardiac magnetic resonance imaging

When CMR contrast agents are used in doses producing equal attenuation as iodinated contrast agents, the risk of renal dysfunction is similar to that caused by iodinated agents.^{31,32} Furthermore, gadolinium-based contrast agents are associated with the development of nephrogenic systemic fibrosis (NSF). Nephrogenic systemic fibrosis is potentially a lethal disease but it has never been seen in patients with normal kidney function.³³ Although rare, acute allergy-like reactions occur after intravenous gadolinium-based contrast agents in 0.03–0.2% of patients.^{34,35} Most reactions are mild (rash, urticaria). Severe, life-threatening reactions (respiratory distress, cardiopulmonary arrest) are extremely rare: only 33 reactions after 687 000 doses³⁶ and very few of them fatal reactions.³⁷

In the present analysis, we estimated a risk for acute fatal events to be 1/1 000 000 studies and the rate of acute severe AEs 4.8/100 000 studies. Since the literature does not present hard data for the calculation of a long-term nephrotoxic risk, we used the same risk factors as those for CT contrast agents. Thus, the estimated long-term death rate was 6.6/10 000 due to nephrotoxicity and 0.33/10 000 due to NSF. The former risk may be overestimated due to fact that smaller amounts of contrast materials are used.

Tracers for radionuclide imaging

Radiotracers for cardiac imaging (SPECT or PET) have good safety profiles: 2–6 AEs/million for ^{99m}Tc-sestamibi/-tetrofosmin injections.^{38–40} The risk of AEs is even lower with ²⁰¹thallium. No serious AEs have been reported after PET tracers. The overall the prevalence of AEs following radiopharmaceutical administration is >1000 times lower than that after ordinary pharmaceuticals and diagnostic contrast media^{38–40} probably related to the very small amount of tracer injected.

For the current risk analysis, the risk of death was considered to be negligible and the rate of serious AEs 0.06/10 000 studies.

Ionizing radiation

The harmful effects of ionizing radiation are classified into stochastic effects, which are due to radiation-induced mutations, and deterministic effects, which are due to radiation-induced cell death. Stochastic effects are the primary concern in cardiac imaging.³

Estimation of the risk from ionizing radiation is difficult, since no prospective trials focusing on the AEs of radiation with doses used in diagnostic procedures have ever been performed. Risks related to low doses are derived by linear extrapolation, mainly from epidemiological studies of atom bomb survivors in Hiroshima and Nagasaki.⁴¹ Currently, one in three women and one in two men in the USA will develop cancer in his or her lifetime.⁴² Since this is so

Table 2 Typical effective doses of the most common cardiac imaging procedures

Procedure	Effective doses (mSv)
Calcium score	1–2
CT angiography	3–20 (mean 7)
TL-201 stress + rest SPECT	22
Tc-99 m tetrofosmin or sestamibi stress + rest SPECT	10
PET perfusion stress + rest (Rb-82, N-13 ammonia, O-15 water)	2.0–2.7
FDG PET viability	4.9
Invasive CAG	2–23 (mean 7)

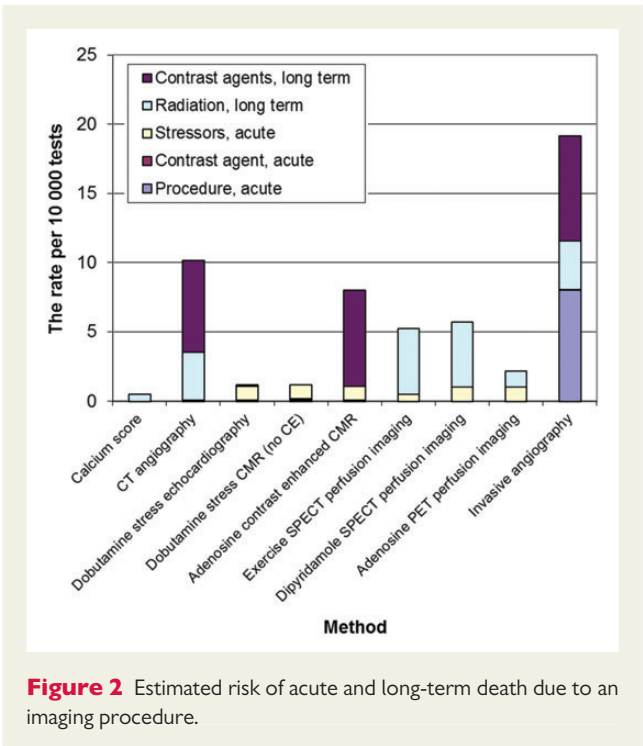
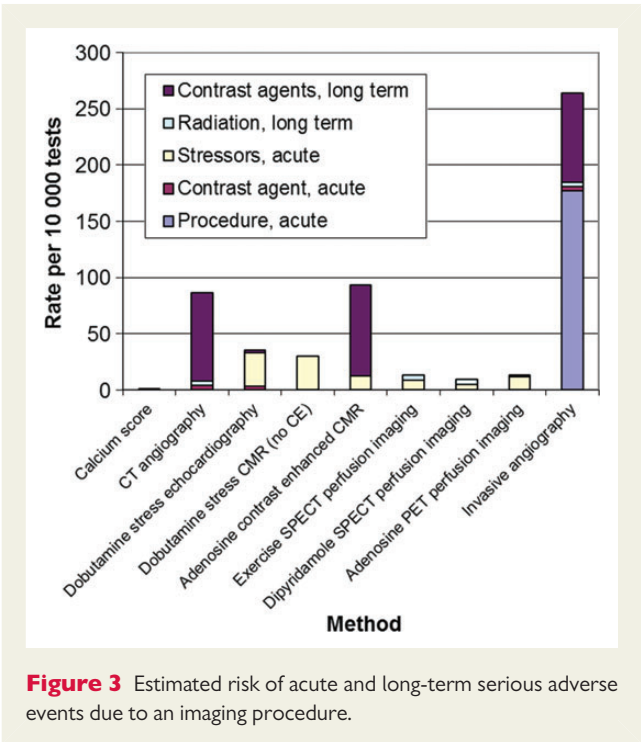
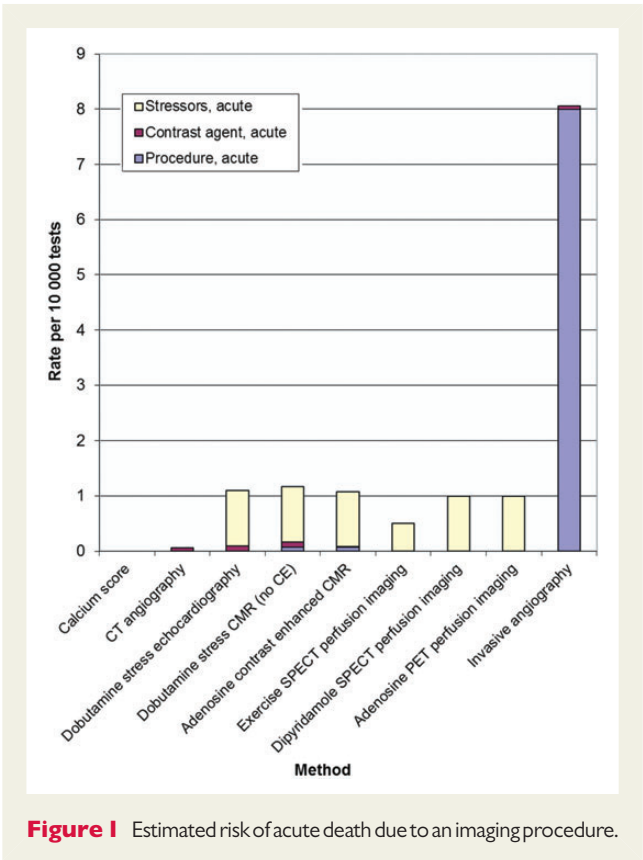
much higher than any estimated effect of medical radiation, the potential minute increase in cancer due to radiation is extremely difficult to detect.

The radiation doses of cardiac examinations are displayed in Table 2. Recent software and hardware implementation may have reduced the patient exposition but could not be taken into account here. Since the risk due to radiation depends on several factors in populations, the European Commission Radiation protection guideline⁴³ (2008) makes cautious statement about using collective effective dose estimates in assessing radiation risks to patients by simple application of the nominal probability coefficients derived for a general population. Being aware of these limitations and since no better estimates are available, for the purpose of this study, we used the estimated risk by ICRP,⁴⁴ in which 10 mSv would translate to 5 additional fatal cancers/10 000 patients.

The composite risks of diagnostic tests

The risks can be divided into acute and long-term risks. The acute AEs include allergic reactions of contrast agents, accidents during the scan and arrhythmias induced by stressors as the more important risks. Long-term AEs include malignancies and contrast-induced nephropathy as the more important risks. The risks of acute and late events were calculated separately and then pooled together to create a composite risk. With the numerous variations of each test, the selected tests are serving as examples for the composite risk profile for typical imaging of CAD.

All non-invasive tests show a very low risk of acute death (Figure 1) and stressors imply the highest risk for death, not the procedures themselves or the contrast agents. The acute risk of an invasive test is related to the procedure itself. When taking into account also



the long-term risks, the picture is somewhat changed (Figure 2). The risks of a fatal event by contrast agents and by radiation exposure are more important using non-invasive tests. The estimated risks of acute

and long-term serious AEs due to an imaging procedure are shown in Figure 3.

Comparison of risks of diseases, therapies and activities of daily life in healthy subjects

In Figure 4, the composite long-term risks of a fatal event due to imaging are compared with the risks of CAD, aspirin medication and the risks of daily-life activities. Based on SCORE,⁴⁵ an asymptomatic male at the age of 50–60 years with more than one risk factor for atherosclerosis has a 10-year risk of cardiovascular death ~1000/10 000. In a symptomatic population, the risk will definitely be higher and dependent on the severity of disease. The life-time risk of fatal bleeding by aspirin medication is 140/10 000.⁴⁶ The life-time risk of dying in a fatal motor vehicle accident is 119/10 000.⁴⁷ The corresponding risks of fatal accidents for pedestrians, by drowning and by bicycling, are 16, 9 and 2 per 10 000 subjects, respectively. The risk of fatal bleeding due to aspirin is about seven times higher than the risk of an invasive imaging test and 14–280 higher than any non-invasive imaging test. Correspondingly, the risk of death due to CAD even within 10 years is about 50 times higher than the risk of an invasive imaging and 100–2000 times higher than any non-invasive imaging procedure.

Discussion

To the best of our knowledge, this is the first study that has analysed acute and long-term composite risks related to CVI. Our analysis shows several important findings: stress agents are relatively major contributors to acute risks related to CVI. However, in absolute figures, the risk is small. In invasive tests, the procedure itself is the most important risk factor. For long-term risks of fatal events, the

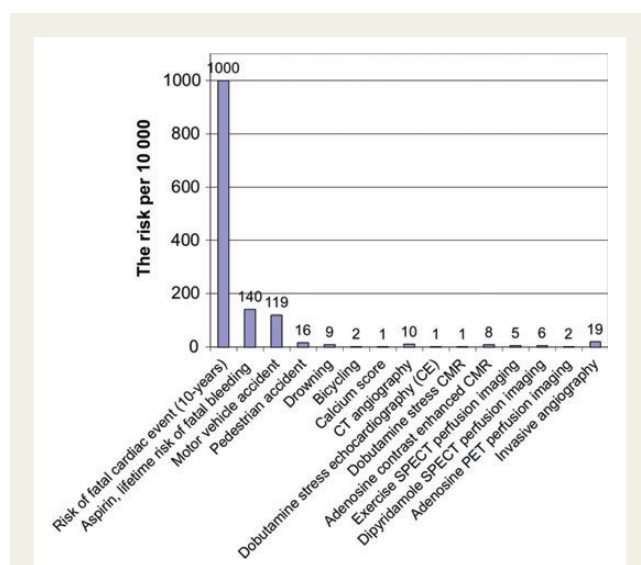


Figure 4 Risk of fatal events after imaging compared with other risks. The graph displays the risks of fatal cardiac events in asymptomatic 50- to 60-year-old men with more than one risk factor for atherosclerosis, fatal bleeding during aspirin therapy, risk of fatal events due to selected activities in daily life, and fatal events after cardiovascular imaging procedures.

risks of contrast agents and the radiation risk have high impact on the composite risk of the procedure. The risks of non-fatal events are mostly related to stressors and contrast agents.

It is to be noted that the life-time risk of imaging procedures for fatal events is small as compared with the general risk of fatal cardiac events by CAD both in asymptomatic and symptomatic populations. Although the risk of aspirin therapy has no clear link with the risks of imaging test, we used that for a comparison to get an idea about the scale of various risks. Aspirin therapy is commonly suggested as a safe therapy for patients with coronary atherosclerosis and is used liberally in patients with mild and asymptomatic CAD. We found that the risk of imaging tests at the highest is less than one-seventh of the life-time risk of fatal bleeding by aspirin. The risk associated with revascularization is of course markedly higher than any medical or diagnostic intervention but the benefit is also well documented when used appropriately.

The risk associated with imaging procedures is small as compared also with other risks. In patients with suspected or known CAD, the risks from the disease left untreated is obviously much higher and increases with the severity of the disease. Therefore, the relative risk from the natural course of the disease as compared with the risk of imaging is even more striking. The relative low risk of imaging is further emphasized when comparing risks of imaging tests with daily-life activities and imaging risk appears in the same range as that related to walking, swimming, or bicycling.

The benefit of imaging, both in known and suspected CAD, is presently intensively debated: What is the best algorithm for demonstrating CAD in order to offer a therapeutic intervention? The economic consequences of the recent increases in number of imaging procedures also play a significant role in the debate. There is no doubt

that benefit of imaging is not only achieved, but indispensable for patients, both to offer optimal therapeutic interventions and to eliminate the fear and anxiety in symptomatic subjects without CAD.

Conclusions

The CVI tests are all related to small but detectable risks. Different components of imaging tests contribute to the acute and long-term risks. The composite risks of imaging tests are in the same range as the risks of common daily-life activities and are only a minor fraction of the risk of CAD or common therapeutic or prophylactic medical interventions.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Funding

The study was supported by the Centre of Excellence in Molecular Imaging in Cardiovascular and Metabolic Research, supported by the Academy of Finland, University of Turku, Turku University Hospital, and Abo Academy. Financial support was also obtained from the Finnish Cardiovascular Foundation and the Hospital, District of South-west Finland.

Conflict of interest: This study is published on behalf of the European Council of Nuclear Cardiology, a joint Council of European Association of Nuclear Medicine and European Society of Cardiology Working Group on Nuclear Cardiology and Cardiac CT.

References

- Brenner DJ, Hall EJ. Current concepts – computed tomography – an increasing source of radiation exposure. *N Engl J Med* 2007;**357**:2277–2284.
- Lauer MS. Elements of danger – the case of medical imaging. *N Engl J Med* 2009;**361**:841–843.
- Fazel R, Krumholz HM, Wang YF, Ross JS, Chen J, Ting HH, Shah ND, Nasir K, Einstein AJ, Nallamothu BK. Exposure to low-dose ionizing radiation from medical imaging procedures. *N Engl J Med* 2009;**361**:849–857.
- Organization WH. Safety of Medicines. A guide to detecting and reporting adverse drug reactions. Why health professionals need to take action. http://whqlibdoc.who.int/hq/2002/WHO_EDM_QSM_2002.2.pdf 2002.
- Myers J, Voodi L, Umann T, Froelicher VF. A survey of exercise testing: methods, utilization, interpretation, and safety in the VAHCS. *J Cardiopulm Rehabil* 2000;**20**:251–258.
- Stuart RJ Jr, Ellestad MH. National survey of exercise stress testing facilities. *Chest* 1980;**77**:94–97.
- Cerqueira MD, Verani MS, Schwaiger M, Heo J, Iskandrian AS. Safety profile of adenosine stress perfusion imaging: results from the Adenoscan Multicenter Trial Registry. *J Am Coll Cardiol* 1994;**23**:384–389.
- Lette J, Tatum JL, Fraser S, Miller DD, Waters DD, Heller G, Stanton EB, Bom HS, Leppo J, Nattel S. Safety of dipyridamole testing in 73,806 patients: the Multicenter Dipyridamole Safety Study. *J Nucl Cardiol* 1995;**2**:3–17.
- Cerqueira MD, Nguyen P, Staehr P, Underwood SR, Iskandrian AE. Effects of age, gender, obesity, and diabetes on the efficacy and safety of the selective A2A agonist regadenoson versus adenosine in myocardial perfusion imaging integrated ADVANCE-MPI trial results. *JACC Cardiovasc Imaging* 2008;**1**:307–316.
- Lattanzi F, Picano E, Adamo E, Varga A. Dobutamine stress echocardiography: safety in diagnosing coronary artery disease. *Drug Saf* 2000;**22**:251–262.
- Bruder O, Schneider S, Nothnagel D, Dill T, Hombach V, Schulz-Menger J, Nagel E, Lombardi M, van Rossum AC, Wagner A, Schwitzer J, Senges J, Sabin GV, Sechtem U, Mahrholdt H. EuroCMR (European Cardiovascular Magnetic Resonance) registry: results of the German pilot phase. *J Am Coll Cardiol* 2009;**54**:1457–1466.
- Shellock FG. Radiofrequency energy-induced heating during MR procedures: a review. *J Magn Reson Imaging* 2000;**12**:30–36.
- Levine GN, Gomes AS, Arai AE, Bluemke DA, Flamm SD, Kanal E, Manning WJ, Martin ET, Smith JM, Wilke N, Shellock FS. Safety of magnetic resonance imaging in patients with cardiovascular devices: an American Heart Association scientific

- statement from the Committee on Diagnostic and Interventional Cardiac Catheterization, Council on Clinical Cardiology, and the Council on Cardiovascular Radiology and Intervention: endorsed by the American College of Cardiology Foundation, the North American Society for Cardiac Imaging, and the Society for Cardiovascular Magnetic Resonance. *Circulation* 2007;**116**:2878–2891.
14. Schaefer DJ, Bourland JD, Nyenhuis JA. Review of patient safety in time-varying gradient fields. *J Magn Reson Imaging* 2000;**12**:20–29.
 15. Simi S, Ballardini M, Casella M, De Marchi D, Hartwig V, Giovannetti G, Vanello N, Gabbriellini S, Landini L, Lombardi M. Is the genotoxic effect of magnetic resonance negligible? Low persistence of micronucleus frequency in lymphocytes of individuals after cardiac scan. *Mutat Res* 2008;**645**:39–43.
 16. Fiechter M, Stehli J, Fuchs TA, Dougoud S, Gaemperli O, Kaufmann PA. Impact of cardiac magnetic resonance imaging on human lymphocyte DNA integrity. *Eur Heart J* 2013;**34**:2340–2345.
 17. Andreassi MG, Venneri L, Picano E. Cardiac imaging: the biological effects of diagnostic cardiac ultrasound. *Prog Biophys Mol Biol* 2007;**93**:399–410.
 18. Duck FA. Hazards, risks and safety of diagnostic ultrasound. *Med Eng Phys* 2008;**30**:1338–1348.
 19. Miller DL, Qudus J. Diagnostic ultrasound activation of contrast agent gas bodies induces capillary rupture in mice. *Proc Natl Acad Sci USA* 2000;**97**:10179–10184.
 20. Scanlon PJ, Faxon DP, Audet AM, Carabello B, Dehmer GJ, Eagle KA, Legako RD, Leon DF, Murray JA, Nissen SE, Pepine CJ, Watson RM, Ritchie JL, Gibbons RJ, Chaitlin MD, Gardner TJ, Garson A Jr, Russell RO Jr, Ryan TJ, Smith SC Jr. ACC/AHA guidelines for coronary angiography: executive summary and recommendations. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Coronary Angiography) developed in collaboration with the Society for Cardiac Angiography and Interventions. *Circulation* 1999;**99**:2345–2357.
 21. Tavakol M, Ashraf S, Brenner SJ. Risks and complications of coronary angiography: a comprehensive review. *Glob J Health Sci* 2012;**4**:65–93.
 22. Cohan RH, Ellis JH, Garner WL. Extravasation of radiographic contrast material: recognition, prevention, and treatment. *Radiology* 1996;**200**:593–604.
 23. Namasivayam S, Kalra MK, Torres WE, Small WC. Adverse reactions to intravenous iodinated contrast media: a primer for radiologists. *Emerg Radiol* 2006;**12**:210–215.
 24. McCullough PA, Stacul F, Becker CR, Adam A, Lameire N, Tumlin JA, Davidson CJ. Contrast-Induced Nephropathy (CIN) Consensus Working Panel: executive summary. *Rev Cardiovasc Med* 2006;**7**:177–197.
 25. Nash K, Hafeez A, Hou S. Hospital-acquired renal insufficiency. *Am J Kidney Dis* 2002;**39**:930–936.
 26. McCullough PA. Contrast-induced acute kidney injury. *J Am Coll Cardiol* 2008;**51**:1419–1428.
 27. James MT, Samuel SM, Manning MA, Tonelli M, Ghali WA, Faris P, Knudtson ML, Pannu N, Hemmelgarn BR. Contrast-induced acute kidney injury and risk of adverse clinical outcomes after coronary angiography: a systematic review and meta-analysis. *Circ Cardiovasc Interv* 2013;**6**:37–43.
 28. Main ML, Goldman JH, Grayburn PA. Ultrasound contrast agents: balancing safety versus efficacy. *Expert Opin Drug Saf* 2009;**8**:49–56.
 29. Asch FM, Weissman NJ. Overview of the 2008 Food and Drug Administration Advisory Committee on safety considerations in the development of ultrasound contrast agents. *Circulation* 2009;**119**:1956–1961.
 30. Document FACB. Definity Premier Database Study. <http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4369b1-00-index.html> 2008.
 31. Boyden TF, Gurm HS. Does gadolinium-based angiography protect against contrast-induced nephropathy?: a systematic review of the literature. *Catheter Cardiovasc Interv* 2008;**71**:687–693.
 32. Perazella MA. Current status of gadolinium toxicity in patients with kidney disease. *Clin J Am Soc Nephrol* 2009;**4**:461–469.
 33. Kribben A, Witzke O, Hillen U, Barkhausen J, Daul AE, Erbel R. Nephrogenic systemic fibrosis: pathogenesis, diagnosis, and therapy. *J Am Coll Cardiol* 2009;**53**:1621–1628.
 34. Dillman JR, Ellis JH, Cohan RH, Strouse PJ, Jan SC. Frequency and severity of acute allergic-like reactions to gadolinium-containing i.v. contrast media in children and adults. *Am J Roentgenol* 2007;**189**:1533–1538.
 35. Prince MR, Zhang H, Zou Z, Staron RB, Brill PW. Incidence of immediate gadolinium contrast media reactions. *Am J Roentgenol* 2011;**196**:W138–W143.
 36. Murphy KP, Szopinski KT, Cohan RH, Mermillod B, Ellis JH. Occurrence of adverse reactions to gadolinium-based contrast material and management of patients at increased risk: a survey of the American Society of Neuroradiology Fellowship Directors. *Acad Radiol* 1999;**6**:656–664.
 37. Jordan RM, Mintz RD. Fatal reaction to gadopentetate dimeglumine. *AJR Am J Roentgenol* 1995;**164**:743–744.
 38. Silberstein EB. Prevalence of adverse reactions to positron emitting radiopharmaceuticals in nuclear medicine. Pharmacopeia Committee of the Society of Nuclear Medicine. *J Nucl Med* 1998;**39**:2190–2192.
 39. Hesslewood SR, Keeling DH. Frequency of adverse reactions to radiopharmaceuticals in Europe. *Eur J Nucl Med* 1997;**24**:1179–1182.
 40. Silberstein EB, Ryan J. Prevalence of adverse reactions in nuclear medicine. Pharmacopeia Committee of the Society of Nuclear Medicine. *J Nucl Med* 1996;**37**:185–192.
 41. Preston DL, Ron E, Tokuoka S, Funamoto S, Nishi N, Soda M, Mabuchi K, Kodama K. Solid cancer incidence in atomic bomb survivors: 1958–1998. *Radiat Res* 2007;**168**:1–64.
 42. Siegel R, DeSantis C, Virgo K, Stein K, Mariotto A, Smith T, Cooper D, Gansler T, Lerro C, Fedewa S, Lin C, Leach C, Cannady RS, Cho H, Scoppa S, Hachey M, Kirch R, Jemal A, Ward E. Cancer treatment and survivorship statistics, 2012. *CA Cancer J Clin* 2012;**62**:220–241.
 43. Directorate-General for Energy and Transport DHNEUH, European Commission. RADIATION PROTECTION N° 154, European Guidance on Estimating Population Doses from Medical X-Ray Procedure. http://ec.europa.eu/energy/nuclear/radiation_protection/publications_en.htm 2008 (20 March 2013, date last accessed).
 44. Protection ICoR. Radiation and your patient: a guide for medical practitioners. A web module produced by Committee 3 of the International Commission on Radiological Protection. www.icrp.org/docs/Rad_for_GP_for_web.pdf 2011 (20 March 2013, date last accessed).
 45. Conroy RM, Pyorala K, Fitzgerald AP, Sans S, Menotti A, De Backer G, De Bacquer D, Ducimetiere P, Jousilahti P, Keil U, Njolstad I, Oganov RG, Thomsen T, Tunstall-Pedoe H, Tverdal A, Wedel H, Whincup P, Wilhelmsen L, Graham IM. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. *Eur Heart J* 2003;**24**:987–1003.
 46. Saini SD, Schoenfeld P, Fendrick AM, Scheiman J. Cost-effectiveness of proton pump inhibitor cotherapy in patients taking long-term, low-dose aspirin for secondary cardiovascular prevention. *Arch Intern Med* 2008;**168**:1684–1690; discussion 1691.
 47. Lifetime odds of death for selected causes. United States 2006. Lifetime odds of death for selected causes. United States 2006. NATIONAL SAFETY COUNCIL® INJURY FACTS 2010 EDITION.